EXHIBIT I

PATENT
Attorney Docket No. 182.0001-US00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)
Michael FRANCIS, et al.	) Confirmation No. 6860
Application No: 16/152,963	) Group Art Unit: 1613
Filed: October 5, 2018	) Examiner: SONG, Jianfeng
For: BIOPOLYMER COMPOSTIONS, SCAFFOLDS AND DEVICES	) Date: September 6, 2019

AMENDMENT AND RESPONSE TO ACCOMPANY RCE

Commissioner for Patents
United States Patent and Trademark Office
MAIL STOP: AMENDMENT
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Commissioner:

In response to the Final Office Action dated April 10, 2019, and the Applicant Initiated Interview Summary dated June 11, 2019, Applicants respectfully request reconsideration of this application in view of the following amendments and remarks. A two-month extension of time accompanies this response. Please amend this application as follows:

Amendments to the Claims begin on page 2.

Remarks begin on page 5.

AMENDMENTS

IN THE CLAIMS:

This listing of claims replaces all prior listings or versions of claims in the present application.

(Claims 1-36 are cancelled.)

37. (New) An implantable ligament and tendon repair device comprising,

a biopolymer sheet formed of substantially aligned electrospun biopolymer fibers;

wherein the biopolymer fibers comprise about 10 to 35% by weight of Type I collagen and about 65 to 90% by weight of a synthetic polymer selected from the group consisting of PLLA, PDLA, PDLLA, PLGA and mixtures thereof; and

wherein the biopolymer fibers are not chemically cross-linked;

wherein the biopolymer sheets are annealed; and

wherein the ligament and tendon repair device has biomechanical characteristics supportive of native human tendons and ligaments.

38. (New) The implantable ligament and tendon repair device of claim 37, wherein the biopolymer fibers further comprise about 20 to 35% by weight of Type I collagen and ~~a~~bout 65 to 80% by weight of synthetic polymer.

39. (New) The implantable ligament and tendon repair device of claim 38, wherein the biopolymer fibers further comprise about 27.5 to 32.5% by weight of Type I collagen and about 67.5 to 72.5% by weight of the synthetic polymer.

40. (New) The implantable ligament and tendon repair device of claim 38, wherein the Type I collagen is selected from the group consisting of atelocollagen, telocollagen, recombinant human collagen and mixtures thereof.

41. (New) The implantable ligament and tendon repair device of claim 39, wherein the Type I collagen is selected from the group consisting of atelocollagen, telocollagen, recombinant human collagen and mixtures thereof.

42. (New) The implantable ligament and tendon repair device of claim 40, wherein the synthetic polymer is PDLLA having an inherent viscosity of about 0.55 dL/g-4.5 dL/g or higher.

43. (New) The implantable ligament and tendon repair device of claim 41, wherein the synthetic polymer is PDLLA having an inherent viscosity of about 0.55 dL/g-4.5 dL/g or higher.

44. (New) The implantable ligament and tendon repair device of claim 42, wherein the biopolymer sheet has a thickness of about 0.2 mm or about 0.4 mm.

45. (New) The implantable ligament and tendon repair device of claim 43, wherein the biopolymer sheet has a thickness of about 0.2 mm or about 0.4 mm.

46. (New) The implantable ligament and tendon repair device of claim 38, wherein the biopolymer sheet of the ligament and tendon repair device exhibits one or more of the characteristics selected from the group consisting of:

(i) a range of tensile strength of about 4 to 16 MPa;

(ii) a modulus of elasticity of about 35-750 MPa; and

(iii) a peak stress of about 11 to 15.2 MPa.

(iv) a strain to failure of 50-200% (0.5 to 2.0 mm/mm) as tensile tested at 1 mm/s in hydrated condition.

47. (New) The implantable ligament and tendon repair device of claim 39, wherein the biopolymer sheet of the ligament and tendon repair device exhibits one or more of the characteristics selected from the group consisting of:

(i) a range of tensile strength of about 4 to 16 MPa;

(ii) a modulus of elasticity of about 35-200 MPa; and

(iii) a peak stress of about 11 to 15.2 MPa.

(iv) a strain to failure of 50-200% (0.5 to 2.0 mm/mm) as tensile tested at 1 mm/s in hydrated condition.

48. (New) The implantable ligament and tendon repair device of claim 42, wherein the biopolymer fibers of the biopolymer sheet have an average diameter of 700 nm to 1,500 nm.

49. (New) The implantable ligament and tendon repair device of claim 43, wherein the biopolymer fibers of the biopolymer sheet have an average diameter of 700 nm to 1,500 nm.

50. (New) The implantable ligament and tendon repair device of claim 42, wherein the ligament and tendon repair device is seeded with tenocytes prior to implantation.

51. (New) The implantable ligament and tendon repair device of claim 43, wherein the ligament and tendon repair device is seeded with tenocytes prior to implantation.

52. (New) The implantable ligament and tendon repair device of claim 42, in a form selected from the group consisting of a wrap and an onlay.

53. (New) The implantable ligament and tendon repair device of claim 43, in a form selected from the group consisting of a wrap and an onlay.

54. (New) The implantable ligament and tendon repair device of claim 52, comprising more than one biopolymer sheet.

55. (New) The implantable ligament and tendon repair device of claim 53, in a form comprising more than one sheet.

REMARKS

1. The Status of the Claims

The original claims have been canceled and new independent claim 37 and new dependent claims 38 - 55 are submitted to more clearly distinguish Applicant's invention. The Examiner's observations during the telephonic interview were helpful in making these clarifications.

Support for these new claims appears throughout the specification, for example, the implantable ligament and tendon repair device in the preamble is described in Para. 0012, 0022 and 0059. Providing a device having "characteristics supportive of native human tendons and ligaments" is a key object of the invention as is described in Para. 0030. These characteristics include implants "having a tensile strength, flexibility, modulus of elasticity and other biomechanical characteristics supportive of native human tendons" as are described throughout the specification including Para. 0051.

The claimed ratios of biopolymer fiber components are described in Para. 0013 and original claims 2 and 3; synthetic polymers are described in Para. 0010 and original claim 1; alignment of fibers is described in Para. 0019 and 0029 and original claim 1; thermal annealing of the biopolymer sheets is described as a post-processing step at Para. 0058; and a preferred embodiment in which fibers are not cross-linked in described in Para. 0049.

The use of a high molecular weight PDLLA is defined at Para. 0027 as having an inherent viscosity of about 0.55 dL/g-4.5 dL/g or higher. And ranges of as-spun fiber diameters are described at Para. 0018 and 0051 and original claims 9 - 11. Particular embodiments of the device, such as wraps, sheets, meshes and an onlay, are described in Para. 0065.

Applicant wishes to call the Examiner's attention to its copending application SN 16/222,350, presently being examined in Art Unit 1742. The application discloses implantable devices for the repair of soft tissue injuries having a fiber composition similar to the claims in the instant application.

2. The Telephonic Interview

Applicant thanks Examiner Song for the courtesy of a telephonic interview on June 6, 2019. As discussed, this Amendment accompanies a Request for Continuing Examination. Potential changes to the claim's preamble were discussed as well as the potential addition of a limitation relating to the properties of the device and a limitation excluding cross-linking of the biopolymer fibers. The Examiner's

courteous agreement to phone the undersigned before issuing another office action is acknowledged with appreciation.

3. Objection to the Claim Format

As requested by the previous Office Action, all dependent start with the word "The." Applicant respectfully submits that this objection is moot and may be withdrawn.

4. Rejection for Obviousness Under 35 U.S.C. § 103

The previously pending claims were rejected under 35 U.S.C. § 103 as being unpatentably obvious over Qiao et al. ("Composition and in Vitro Evaluation of Nonwoven Type I Collagen/Poly-dl-lactic Acid Scaffolds for Bone Regeneration", J. Funct. Biomater. 2015, 6, 667-686 in view of Francis et al. (US2016002865), Demirbilek et al. ("Oxidative Stress Parameters of L9292 Cells Cultured on Plasma-Modified PDLLA Scaffolds" Appl. Biochem. Biotechnol. (2011) 164:780-792), Chong et al. (US20090202616) and Hossainy et.al. (US201500081000). Applicant traverses the rejection of record as might be applied to the newly presented claims for the following reasons.

A. *Consideration of Applicant's "Claimed Invention as a Whole" as Required by 35 USC 103*

New independent claim 37 is directed to an **implantable ligament and tendon repair device.** And the body of the claim states that the ligament and tendon repair device has biomechanical characteristics supportive of native human tendons and ligaments Previously, the preamble to claim 1 recited a scaffold "for supporting the repair of a soft tissue injury." The Office Action considered this to be a non-limiting statement of intended use. Without acquiescing in that conclusion, the amendments reflect in new claim 37 should moot this question.

The claimed device was designed with a **fiber composition** that provides the tensile strength, flexibility, modulus of elasticity and other mechanical and biological characteristics supportive of native human ligaments and tendons. (See Para. 0030.) Moreover, the claimed invention is made from one or more biopolymer sheets formed of **substantially aligned and electrospun biopolymer fibers**. These fibers comprise about 10 to 35% by weight of Type I collagen and about 65 to 90% by weight of a

synthetic polymer selected from the group consisting of PLLA, PDLA, PDLLA, PLGA and mixtures thereof. Also, the claimed biopolymer sheets are **annealed** and their biopolymer fibers are **not crosslinked**.

Applicant's invention was made in the course of a rigorous experimental analysis of various implant compositions, which evaluated various types of collagen and numerous blends of collagen with various polymers in order to optimize their properties. (See Para. 0034.) Applicant considered several properties including strength, stability, brittleness, elasticity, and lifespan in vivo and presented relevant data. (See Para. 0036 – 0042.) **The newly-presented claims reflect Applicant's selection of fiber blends that optimize the ligament and tendon repair device**.

The claimed invention also requires that the biopolymer sheets of the ligament and tendon repair device be annealed. Applicant experimentally determined that this post-processing step (that is, after generating and collecting the electroprocessed sheets) changed "fiber diameter, fiber alignment, and void fraction or porosity of the resulting scaffold" (Para. 0058.) This aspect of the invention is part of the claimed subject matter taken as a whole, which is to provide a device having the tensile strength, flexibility, modulus of elasticity and other mechanical and biological characteristics supportive of native human ligaments and tendons.

With respect to certain of the dependent claims, the specification explains that an **amorphous mixture referred to as poly-DL-lactide or PDLLA was the preferred synthetic polymer**:

> *The present inventors have found that **PDLLA is surprisingly effective** for producing fibers and implantable support devices when blended with Type 1 collagen for the uses described in this specification.* [Para. 0041 and Table 1, emphasis added.]

A preferred embodiment of the invention uses a **high molecular weight (or high viscosity) PDLLA**. This polymer is not simply interchangeable with a lower molecular weight (lower viscosity) PDLLA. Applicant determined that this polymer species "led to an increase in the peak stress and modulus of elasticity of the constructs. Accordingly, the high molecular weight (HMW) PDLLA is preferred." (Para. 0034.)

With respect to other of the dependent claims, Applicant's invention reflects a choice in the **diameter of fibers** incorporated into a biopolymer sheet **that optimizes the biological function of the device, in combination with the claimed fiber compositions and post-processing annealing**. The claimed combinations of elements:

> *permit host cell and tissue ingrowth and also vascularization of the scaffold. Over time, the scaffold is absorbed and replaced by a patient's own tissues through a*

remodeling process or is otherwise dissolved, degraded and ultimately removed.

[Para. 0062.]

B. *Scope and Content of the Prior Art*

Before discussing the relevance of the combined references to the new claims, this section addresses these references individually to clarify what they actually disclose to a person of skill in the art. Applicant does not intend to "attack" the references individually (a criticism raised at p. 14 of the Office Action) but rather to discuss what each reference fairly contributes when they are taken in combination. Respectfully, Applicant disagrees with the conclusory discussion of the "difference between the prior art and claims" found at p. 6 of the Office Action and parts of the discussion of the references at pp. 3 - 6.

1. Qiao.

Regarding Qiao, the primary reference, the Office Action appears to make conclusions about Qiao that are not factually supportable. For example:

Page 9 of the Office Action states that Qiao "teaches [a] fiber scaffold for bone regeneration." Notwithstanding the article's title, Qiao actually describes relatively small laboratory samples of randomly oriented, chemically crosslinked and interconnected electrospun fiber scaffolds that were produced to **compare** Type I collagen and gelatin blends for **potential use** for bone regeneration. Qiao tested small circular samples (22 mm in diameter) punched from electrospun scaffolds (p. 680) that were tested in 12-well plates under certain cell culture conditions. In contrast, **Applicant's device is described for implantation in a human subject** in a substantially larger configuration, for example 4 cm x 7 cm (see Para. 0019 and other dimensions at Para. 0064), in order to provide effective support to repair soft tissue damage. Qiao does not actually teach that its punched discs are to be implanted to regenerate bone or even mention the word "implant."

Page 9 states that "the combination of prior arts teaches the same or substantially same implantable scaffold." Although this is the ultimate conclusion regarding obviousness, looking just at Qiao for the moment, Applicant notes that in order to combine pieces of the references to approximate the claimed invention, a person skilled in the art would have to ignore the express teachings of Qiao. For example, Qiao produces an "interconnected porous network" and states that "chemical **crosslinking**

was essential to ensure long term material cell culture" as was noted by the Office Action at p. 4, emphasis added. In contrast, Applicant's claims require that the fibers in the ligament and tendon repair device are **not** crosslinked. Thus, the components of Applicant's device are not interconnected in the manner described by Qiao as necessary to achieve stability and cell growth. There is no suggestion or apparent tolerance in Qiao for uncrosslinked fibers even for cell growth related to bone regeneration.

Page 10 states that Applicant's intended use "is inherent in the reference composition." As noted above, the claims were amended to define a particular **device** with recited elements – that when taken as a whole – goes beyond just having a particular fiber composition. Qiao says nothing about making a ligament and tendon repair device or the requirements of such a device supportive of human tendons and ligaments. And there is no basis in Qiao from which to find that a person skilled in the art would consider a fiber scaffold, potentially and theoretically relevant to bone regeneration, to inherently satisfy the physical and biological requirements of an implanted **ligament and tendon repair device** that has characteristics supportive of native human tendons and ligaments. The mechanical demands on the device, the interface between device and native tissue, size of implanted device and its stability, cell types and their infiltration into the device, resorption time, anchoring rquirements and the like are meaningfully different to a person skilled in the art.

Page 14 states that "Qiao teaches 40-80% of PDL scaffolds achieved optimized properties." This appears to overstate what the reference discloses. Qiao does determine that a blend of collagen and PDLLA is superior to a blend of gelatin and PDLLA in a one-to-one comparison. However, "optimal" according to Qiao does not extend over this entire range. Moreover, Qiao optimizes stability for cell culture and cell growth, but says nothing about "optimal" compositions for its own contemplated bone regeneration purposes. It simply does not address the kind of optimization of composition and processing claimed by Applicant and detailed in the specification for an implantable ligament and tendon repair device. Moreover, there is no basis in the record from which to conclude that even optimized properties for a potential bone regeneration composition are directly transferable to Applicant's particular ligament and tendon device with a reasonable expectation of success. A person skilled in the art knows that repairing bones is a different objective than repairing ligaments and tendons.

2. Francis

Page 5 of the Office Action correctly notes that Francis teaches a scaffold having aligned fibers. However, Francis does not teach a implantable device for the repair of ligaments and tendons. Moreover, there is nothing in Francis or Qiao that suggests the equivalence and substitution of aligned for nonaligned fibers in the compositions used for Qiao's scaffolds. **Because of the other distinctions discussed above, even making this change in fiber alignment does not provide Applicant's claimed ligament and tendon repair device.**

Where Francis does discuss a specific device, it is either an electrospinning device or a "bone matrix implant" characterized as having being "a volume replacement material for augmentation or reconstruction to replace a whole or part of a bone structure." (Para. 0080.) Qiao does not contemplate the use of a bone matrix even for its own bone repair purposes.

Francis describes a variety of fiber compositions in addition to Type I collagen:

> *In some embodiments, the aligned fiber, electrospun fiber, and/or scaffold comprises collagen type I, bone matrix, adipose extracellular matrix, heart basement membrane extract, heart basement membrane extracellular matrix, placenta basement membrane extract, placenta basement membrane extracellular matrix, brain-derived extracellular matrix, polycaprolactone, a biodegradable polymer, an accessory polymer described herein, or the mixture thereof.* [Para. 0069.]

Francis does not disclose Applicant's claimed blends of collagen and synthetic polymers, let alone any blends of Type I collagen and PDLLA for which the Qiao reference was cited. Where a protein (heart basement membrane or "HBM") is exemplified in a mixture with a polymer, this is polycaprolactone (or "PCL", and its ratio was 90:10 of polymer to protein, which is well above the ratio of polymer to collagen that is described by Qiao as creating adverse changes in the scaffold material. This ratio also is outside the range in Applicant's claims.

Moreover, while this reference does disclose fibers in a broad range of diameters, it does not suggest a collagen fiber blend with the mean diameter of certain of Applicant's dependent claims. Although Francis says that crosslinking may be done in some embodiments, it does not provide any guidance for ignoring Qiao's finding that crosslinking was essential.

Notably, Francis provides no comparison, data or examples regarding the various changes required of a person skilled in the art for Qiao's scaffolds to convert them into Applicant's claimed device. There simply is no express or implied reason in Francis to align the fibers of Qiao.

3. Demirbilek

Page 7 of the Office Action correctly notes that Demirbilek discloses 300 MW PDLLA. However, there is no factual basis for the conclusion at p. 7 of the Office Action that Demirbilek suggests the suitability of high molecular weight PDLLA in either the scaffolds of Qiao or in Applicant's ligament and tendon repair device.

The Office Action appears to refer to this statement at p. 781 in Demirbilek that:

> *PDLLA is expected to have wide applications not only as a biodegradable plastic but also as a biomedical material [5, 6] due to its excellent properties, such as mechanical strength, compatibility, transparency, safety, and adjustable hydrolyzability. As it is degradable in the human body, it is particularly suitable for the application of implants which are used only temporarily for the healing process [7].*

However, merely knowing that PDLLA is degradable in the human body does not teach or suggest that is appropriate or would be successful in a bone implant or Applicant's claimed ligament and tendon repair device for which durability and resorption is but one of several factors to balance.

Moreover, in that block quote from Demirbilek, above, the implants contemplated by Ref. 7 (submitted in an IDS along with this Amendment) are "human umbilical vein endothelial cells (HUVEC) onto ethylene-vinyl alcohol (EVOH) copolymer films prepared by casting." This description is readily distinguishable by a person skilled in the art from the cell populations and substrates relevant to Applicant's device.

Overall, Demirbilek describes a research study "to investigate the probable oxidative stress, measure its oxidative damage levels on lipids (MDA) and proteins (AOPP), and determine the SOD activities as an antioxidant enzyme in L929 cells cultured on nonmodified and EDA- or PEG-modified PDLLA scaffolds." (P. 782). It describes the measurement of oxidation-related enzymes and the growth of mouse L929 fibroblasts rather than bone cells contemplated by Qiao. There is no discussion of the relevance of those findings to the contemplated use of Qiao's scaffolds.

Additionally, Demirbilek does not teach any blends of collagen and synthetic polymers. In fact, Demirbilek does not mention ligaments or tendons or the requirements and characteristics of a device to support their repair. It also does not discuss fiber alignment. And crosslinking is mentioned only as a result caused by oxidative stress rather than as a tissue engineering choice as was found to be essential to the stability of Qiao's scaffolds.

Notably, Demirbilek provides no comparison, data or examples regarding the successful implantantion of high vs. low molecular weight PDLLA implants to provide any motivation or a reasonable expectation of success to a person skilled in the art to try substituting high molecular weight PDLLA in the formulations of Qiao's scaffolds.

There simply is no express or implied reason in Demirbilek to expect that high MW PDLLA would provide the benefits of Applicant's claimed invention. **As discussed above, this was a surprising finding by Applicant's after extensive testing and analysis.** And Demirbilek does not address the overall kinds of optimization of composition and processing claimed by Applicant and detailed in its specification for an implantable ligament and tendon repair device.

4. Chong.

Chong describes a two-layer wound dressing having a semi-permeable barrier layer such as Tegaderm and a scaffold fiber layer formed by electrospinning fibers. (Abstract.) This reference is discussed at p. 5 of the Office action as teaching that a "scaffold fiber layer may be capable of supporting cell attachment and proliferation therein." Chong does disclose that "the scaffold fiber layer may be capable of supporting cell attachment and proliferation therein" and it lists a variety of cell types including tenocytes, ligament fibroblast cells and bone marrow derived mesenchymal stemlprogenitor cells. (Para. 0065.) However, because the device of Chong is not analogous in form or purpose to the scaffolds of Qiao or to Applicant's implantable device, its disclosure is not directly relevant.

Chong does mention that electrospun fibers can be aligned at Para. 0156 to "rectify" cell and matrix distribution. However, this reference does not describe the repair of soft tissue injuries such as tendons and ligaments. Where Chong mentions fibers comprising two materials, these are not sheets of aligned, non-crosslinked blended fibers as claimed by Applicant, but instead are in the form of a co-axial fiber. (Para. 0058.)

Chong does not provide any motivation to select collagen and does not disclose blends in the ratios claimed by Applicant. Various proteins and polymers are contemplated, including mixtures. (Para. 0052 – 0058.) However, the only blend specifically described was a 50:50 solution of gelatin/TFE and PCL/TFE at Para. 0160.

Also, Chong does not address the kind of optimization of composition and processing claimed by Applicant and detailed in the specification for an implantable ligament and tendon repair device. There simply is no express or implied reason in Chong to extrapolate from the growth of a list of diverse cell types on Chong's construct and to make Applicant's device for its intended purpose of ligament and tendon repair.

5. Hossainy.

Hossainy describes a braided or woven polymeric scaffold deployed on a catheter to support an "anatomical lumen" such as the cavity or duct of a tubular organ found in a blood vessel, urinary tract, and bile duct (Abstract, Para. 0003 and 0143). Although blends of polymers are disclosed (Para. 0125), the reference does not describe scaffolds to support the repair of soft tissue injuries, such as ligaments or tendons. The reference does not mention collagen, and thus also does not disclose collagen-polymer blends.

Hossainy is cited at p. 6 of the Office Action to show that its fibers may be heated to increase their crystallinity, thereby increasing the tensile strength and modulus of the fiber. However, Hossainy does not provide any guidance as to how annealing Applicant's collagen-polymer sheet would contribute to success of a ligament and tendon repair device that balances a variety of physical and biological parameters required for success in use of Applicant's invention. Moreover, Hossainy does not provide any motivation to select the collagen-polymer blends in the ratios claimed by Applicant. There simply is no express or implied reason in Hossainy for a person skilled in the art to expect to achieve the kind of optimization of composition and processing claimed by Applicant and detailed in the specification for an implantable ligament and tendon repair device.

C. *Discussion of the Obviousness Rejection as Applied to Independent Claim 37*

Regarding the ultimate question of obviousness, the Office Action concluded at p. 9 that "the combination of prior arts teaches the same or substantially same implantable scaffold, this same or

substantially same implantable scaffold must have the same properties." Reduced to its essence, the argument made against Applicant's previous claims seems to be that all constructs with collagen and a polymer are the same. Applicant respectfully disagrees that the combination of references, each properly interpreted as discussed above, would have provided a reasonable expectation of success with regard to the newly presented claims.

According to the Manual of Patent Examining Procedure (MPEP) at Section 706.02(j):

> *To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references.*

It is not sufficient for the Office merely to find individual elements of the claimed invention in various prior art documents. Such use of hindsight is not appropriate. The MPEP at Section 2142 further states that "impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art."

It is a fact that Qiao produces small laboratory samples of randomly oriented, chemically crosslinked and interconnected electrospun fibers to compare blend of PDLLA with Type I collagen and with gelatin for potential bone regeneration. Qiao does not assert that its fiber scaffolds should be implanted as a repair device even for bones. Nothing in Qiao teaches or suggests that its fiber constructs would have the claimed biomechanical characteristics required for a device supportive of the repair of native human tendons and ligaments. In fact, Qiao says nothing about repairing ligaments and tendons.

Whether or not the Qiao scaffold actually could function to support soft tissue injuries, there is nothing expressly stated or implied by Qiao to suggest that aligning fibers and not crosslinking them and then annealing scaffolds should be attempted, let alone that doing so would provide a reasonable expectation that the device claimed by Applicant would be successful for its claimed purpose.

The Office Action does not identify anything expressly stated or reasonably implied by any of Francis, Demirbilek, Chong or Hossainy **that such modifications to Qiao should be made** – or that the altered construct reasonably would have been expected to function successfully as a ligament and tendon repair device. The Office Action essentially starts from a proposition that the various scaffolds disclosed by the cited references are functionally the same as Qiao's scaffolds for any intended implantation site, tissue to be repaired or medical purpose. Also, the Office Action does not present any

suggestion in the references that a person skilled in the art should ignore Qiao's admonition that crosslinking is "essential" for stability.

Because the combination of references does not explictly state or reasonably suggest Applicant's invention, a proper rejection must be supported by a "convincing line of reasoning" from the examiner. Respectfully, as applied to the new claims, the reasoning of the Office Action is not convincing. In its discussion of the *prima facie* case beginning at p. 7, the Office Action reasons that modification of Qiao by Francis is "motivated" because aligned fiber is "suitable" for fiber scaffolds. However, Francis does not teach any ligament and tendon repair device with the composition of Applicant's claims. Similarly, the modification of Qiao to use high molecular weight PDLLA based on Demerbilek is also "suitable" according to the Office Action. However, Demirbilek teaches polymer membranes having other compositions and uses rather than for implantable ligament and tendon repair devices. The modification of annealing Qiao's scaffolds per Hossainy is "advantageous" according to the Office Action. However, Hossainy teaches scaffolds of other compositions to treat anatomical lumens. And the use of tenocytes based on Chong again is "suitable" per the Office Action. However, Chong teaches two-layer wound dressings of other compositions. **And, notably, the Office Action provides no convincing reasoning appropriate for the new claims about modifying Qiao by not crosslinking its fibers.**

Respectfully, the line of reasoning presented by the Office Action against the previous claims does not make a *prima facie* case of obviousness against the new claims. It would be improper for the Office simply make hindsight selections of of various aspects of the cited references in isolation to what they fully disclose in order to find elements of the claims. This is particularly so when a primary reference is directed to other purposes and teaches that certain features – that is, crosslinking, which is excluded from Applicant's claims – are essential. Accordingly, withdrawal of the rejections would be appropriate.

D. Evidence in the Record to Refute "Obviousness" for Independent Claim 37

According to the MPEP Section 2142, the Office "bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. If the examiner does not produce a *prima facie* case, the applicant is under no obligation to submit secondary evidence to show nonobviousness." It is Applicant's belief that the Office Action has not made a *prima facie* case of obviousness against the new

independent claim 37 and its dependent claims. Therefor, as a matter of US Patent and Trademark Office procedure, Applicant is not required to provide evidence to the contrary to rebut the obviousness rejection.

However, in order to provide a complete response, Qiao itself provides persuasive evidence that the claimed fiber compositions would not have been obvious for incorporation into Applicant's claimed ligament and tendon repair device when taken as a whole. *See, e.g. In re Kahn*, 441 F.3d 977, 990 (Fed. Cir. 2006) ("A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.").

Applicant acknowledge that Qiao discloses blended fiber samples having ratios of Type I collagen to PDLLA of 60:40, 40:60 and 20:80. However, as discussed above, Qiao does not teach anything about which ratio, if any, would be appropriate for use in a implantable ligament and tendon repair device as claimed by Applicant.

Qiao actually discourages a person skilled in the art from utilizing collagen-PDLLA blends within the ratios of Applicant's claims. For example, Qiao states that the maximum number of cells attracted to its scaffolds occurred at a 40% ratio of PDLLA. This is outside of Applicant's claims and the lowest relative amount of PDLLA that was tested by Qiao. A relevant excerpt follows:

> *The number of cells attracted to PDL40 (Figure 4C and the corresponding column) was significantly higher than the number of cells on the PDL60 (Figure 4B and the corresponding column) and PDL80 scaffolds (Figure 4A and the corresponding column). Cells on PDL40 were closely packed and spread over the solid surface of the fibres, while spherical cells were observed on both the PDL60 and PDL80 scaffolds.* [P. 673.]

In this regard, assuming that maximal cell attraction was important, Qiao leads in a direction divergent from the path taken by the Applicant and the reference fairly teaches away from Applicant's claimed ratio of collagen to polymer.

Also, as discussed in Applicant's previous amendment, hereby incorporated by reference in its entirety, Qiao explains at p. 673 that "a massive adverse change in sample geometry was observed in the PDL80 scaffolds, compared with PDL40 and PDL60, with the samples appearing to have shrunk/degraded and folded in on themselves." Accordingly, Applicant's claimed ranges of 65 to 90% PDLLA (new claim 37) and 65 to 80% PDLLA (new claim 38) encompass the relative amount of PDLLA

that Qiao reported as suffering massive adverse changes. Applicant's range of 67.5 to 72.5% PDLLA (new claim 39) has a lower limit for PDLLA that is above Qiao's 60% ratio. While the 65% of PDLLA in Applicant's claims 37 and 38 is closer to the PDL60 blend of Qiao, the relevant question is whether a person skilled in the art would have been led in a divergent direction from the path taken by Applicant.

The Office Action restated Applicant's previous comments about these adverse changes but did not discuss or refute them. In response to Applicant's arguments, the Office Action **incorrectly stated** at p. 12 that "Qiao teaches 40-80% of PDL scaffolds achieved optimized properties." Respectfully, Applicant does not find this statement in the reference. And a proper rejection must address this teaching of "massive adverse change" in the claimed composition range and provide convincing reasoning against Applicant's own expressed reasoning.

The previous Office Action concluded that Applicant had "failed to demonstrate criticality of about 65 to 80% PDLLA (or 67.5 to 72.5% PDLLA), thus, the 103 rejection is still proper." Respectfully, such a demonstration might be required to rebut a proper *prima facie* case of obviousness when a claimed range is "the difference between the claimed invention and the prior art." (See MPEP Section 2144.05). However, as discussed above, the claimed invention differs from Qiao in several ways other than this composition range. Taking the invention as a whole, Qiao fairly discourages the use of composition blends in Applicant's claimed range.

E. Comments Regarding Certain Dependent Claims

New claims 46 and 47 are independently patentable because they recite certain mechanical parameters that are not taught or suggested by the prior art as relevant to an implantable ligament and tendon device.

New claims 48 and 49 also are independently patentable because they recite a range of as-spun fiber diameters that are not taught or suggested by the prior art as relevant to an implantable ligament and tendon device. The previous Office Action discussed fiber diameter, however, those comments are not believed to be relevant to the new claims when their subject matter as a whole is considered.

5. Conclusion

In view of the above amendments and remarks, Applicant respectfully requests further examination of this application and the timely allowance of the pending claims. Applicant appreciates the Examiner's commitment to telephone the undersigned to expedite further prosecution of this application.

Please grant any extensions of time required to enter this response and charge any additional required fees for this submission to our Deposit Account No. 50-5410.

Respectfully submitted,

J. A. Lindeman & Co. PLLC

By: /Jeffrey A. Lindeman, Reg. No. 34,658/
Jeffrey A. Lindeman, Ph.D. Esq.
Registration No. 34,658

J.A. LINDEMAN & CO. PLLC
3190 Fairview Park Drive, Suite 1070
Falls Church, Virginia 22042
(703) 776-9700